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Perspectives

Microbiome and response to immunotherapy in malignant melanoma

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Abstract

Immune checkpoint inhibitors (ICIs) have improved survival in advanced melanoma; however, a considerable number of patients does not respond, and side effects are common. Studies suggest that the gut microbiome may influence ICI outcomes, with certain bacteria and microbial functions being linked to a positive response in some patient groups. However, findings are inconsistent across studies, and no universal microbial biomarkers have been identified. Longitudinal and multi-omic analyses indicate that microbial dynamics may matter, and that other body sites, such as the skin and the intratumoral environment, could also be relevant. More systematic research and testing of multiple hypotheses is needed before microbiome-based strategies may be reliably applied in clinical practice. Here, we summarize evidence connecting the human microbiome to ICI response in melanoma.

Key words: Melanoma, microbioma, immune checkpoint inhibition

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Introduction

Immune checkpoint inhibition (ICI) has revolutionized treatment outcomes in patients with advanced melanoma [1–4]: The recently published 10-year follow-up results of the CheckMate 067 trial reported a melanoma-specific survival (MSS) rate exceeding 50% in patients treated with the combination of anti-PD-1 and anti-CTLA-4 therapy [4]. Despite these encouraging data a considerable number of patients with advanced melanoma does not show response to anti-PD-1 and/or anti-CTLA-4 treatment regimens [5]; furthermore, ICI can induce multiple immune-related adverse events (irAEs) [6].

Considerable efforts have therefore been undertaken to investigate host and tumor characteristics that modulate ICI efficacy: Among these, the microbiome has emerged as a potential key player in enhancing the effects of anti-PD-1 and/or anti-CTLA-4 therapy. Evidence from preclinical mouse models indicated a strong link between gut microbiome composition and responsiveness to immunomodulatory treatments in cancer [7, 8]. Here, we highlight the emerging

evidence linking the human microbiome to ICI efficacy in melanoma. We also discuss the current gaps in our knowledge and consider the potential implications for future therapeutic strategies.

Gut microbiome

Several landmark observational studies have linked gut microbiome composition with response to ICI in melanoma (Table 1). One of the first studies in this field was conducted by Vétizou et al. [8] and revealed that CTLA-4-inhibition in patients with melanoma can shape the composition of the gut microbiome.

Shortly thereafter, Frankel et al. [9] published the first prospective pilot study on the association of gut microbiome composition and ICI response in metastatic melanoma. They reported that the faecal microbiome of ipilimumab plus nivolumab responders was enriched in certain taxa such as *Faecalibacterium prausnitzii* [9].

The concept of "favourable" and "unfavourable" gut microbiome compositions was further reinforced and widely disseminated by two pivotal cross-sectional studies that caused major interest in this field [10, 11]: Gopalakrishnan et al. [10] showed that alpha diversity (a measure of the diversity within a single sample, considering both richness and evenness of species) and relative abundance of Ruminococcaceae were significantly higher in responders, whereas Matson et al. [11] identified three different species (*Bifidobacterium longum*, *Collinsella aerofaciens*, *Enterococcus faecium*) that were more abundant in ICI responders within their cohort. Both studies also performed faecal microbiota transplantation (FMT) from ICI responders into melanoma mouse models; mice with a responder-derived gut microbiome exhibited enhanced anti-tumor responses compared to controls not receiving FMT [10, 11].

Peters et al. [12] were the first to combine metagenomic with metatranscriptomic analyses in patients with melanoma undergoing ICI, thereby providing the first functional data on how the microbiome might actually influence ICI response. Within their cohort microbial richness and transcriptionally active microbial pathways, including L-rhamnose degradation and B-vitamin biosynthesis, were associated with longer progression-free survival (PFS) [12].

Building on these mechanistic insights, larger observational studies further characterized microbiome–therapy interactions: Spencer et al. [13] reported that higher dietary fiber intake was associated with improved ICI response, whereas probiotic use was linked to impaired ICI efficacy [13]. Responders to anti-PD-1 therapy showed enrichment of Ruminococcaceae and *Faecalibacterium* (including *F. prausnitzii*); however, no significant differences in alpha diversity could be found between responders and non-responders, challenging earlier findings of their own [10, 13]. They explained this discrepancy by the differences in patient numbers and the resulting statistical power [13].

McCulloch et al. [14] underscored this observation of comparable alpha diversity between responders and non-responders through a meta-analysis of microbiome datasets, including a newly collected anti-PD-1-treated melanoma cohort and four previously published cohorts from different geographical regions within the United States (US) [9–12]. They reported that specific taxa from the Lachnospiraceae family and *Bifidobacterium* were enriched in responders, while *Prevotella* species were more common in non-responders [14].

Table 1. Landmark observational clinical trials investigating the association between gut microbiome composition and ICI response in patients with advanced melanoma.

Publication	Patient number	Treatment	Sequencing methods	Study type	Results
Gopalakrishnan et al. Science. 2018 [10]	n = 43	anti-PD-1: n=40 anti-PD-1 combination: n=3[a]	16S rRN shotgun m.*	cross-sectional[b]	Responders have higher gut microbiome diversity and increased Ruminococcaceae; favourable microbiome linked to enhanced systemic and anti-tumor immunity. Faecal transfer from responders improves anti-tumor response in mice.
Matson et al. Science. 2018 [11]	n = 42	anti-PD-1: n=38 anti-CTLA-4: n=4	16S rRNA shotgun m. qPCR	cross-sectional	Specific commensal bacteria (*Bifidobacterium longum*, *Collinsella aerofaciens*, *Enterococcus faecium*) enriched in responders; faecal transfer from responders enhances tumor control and T-cell responses in mice.
Spencer et al. Science. 2021 [13]	n=254[c]	anti-PD-1: n=170 anti-CTLA-4: n=16 anti-PD-1 and anti-CTLA-4: n=68	16S rRNA shotgun m.	cross-sectional	Higher dietary fiber intake is associated with improved PFS in ICI-treated melanoma; probiotic use may impair response. Responders to anti-PD-1 therapy show enrichment of Ruminococcaceae and *Faecalibacterium* (including *F. prausnitzii*), but there are no significant differences in alpha or beta diversity between responders and non-responders.
McCulloch et al. Nature Medicine. 2022 [14]	n=155[d]	anti-PD-1: n=155	16S rRNA shotgun m.	cross-sectional	No difference in alpha diversity between responders and non-responders. Taxa belonging to the Lachnospiraceae family (few genera) and Actinobacteria phylum (incl. *Bifidobacterium*) were enriched in responders; *Prevotella* spp. (Bacteroidetes) was enriched in non-responders.
Lee et al. Nature Medicine. 2022 [15]	n=165	anti-PD-1: n=100 anti-CTLA-4: n=11 anti-PD-1 and anti-CTLA-4: n=54	shotgun m.	cross-sectional	Gut microbiome composition is associated with ICI response, but specific microbial signatures are cohort-dependent; no single species is a universal biomarker; *Bifidobacterium pseudocatenulatum*, *Roseburia* spp., and *Akkermansia muciniphila* enriched in some responders.
Simpson et al. Nature Medicine. 2022 [16]	n=218[e]	anti-PD-1: n=115 anti-PD-1 and anti-CTLA-4: n=103	16S rRNA shotgun m.	cross-sectional	Ruminococcaceae-dominated microbiomes are associated with higher response rates; *Bacteroidaceae* dominance and low fiber/omega-3 intake linked to poor response; geographic and dietary factors influence microbiome-response associations.
Björk et al. Nature Medicine. 2024 [18]	n=175	anti-PD-1: n=117 anti-PD-1 and anti-CTLA-4: n=58	shotgun m.	longitudinal	Distinct microbial genome bins and pathways at baseline and after treatment initiation are associated with PFS≥12 months; dynamic changes in microbiome composition relate to ICI regimen, irAEs, and concomitant medication.

[a] combinations included Abraxane, Urelumab, Aldara cream
[b] 3 patients were sampled longitudinally – no dynamics in microbiota development
[c] of 438 patients included, only 254 had advanced melanoma with ICI and sufficient follow-up; 38 of these 254 patients were from the cohort of Gopalakrishnan et al. [10]
[d] 94 patients' samples were collected for this study, further sequenced samples were from the cohorts of Frankel et al. [9], Gopalakrishnan et al. [10] and Matson et al. [11] and Peters et al. [12]
[e] 103 patients' samples were collected for this study, 115 patients were included from the cohorts of Gopalakrishnan et al. [10] and Matson et al. [11] and Spencer et al. [13]
* shotgun m. = shotgun metagenomic sequencing.

Lee et al. [15] performed a large cross-cohort meta-analysis (n=165) and showed that although gut microbiome composition was consistently associated with ICI response, specific microbial signatures varied across patient cohorts and geographical regions. They reported that certain species were enriched in subsets of responders, but no single taxon emerged as a universal biomarker [15].

In parallel, Simpson et al. [16] analyzed microbiome profiles from 218 patients with advanced melanoma (one Australian, one Dutch and two US

cohorts) and confirmed that Ruminococcaceae-dominated microbiomes were associated with improved response rates; however, this study once more revealed geographically distinct microbial signatures of response. These findings underscore that external factors – such as regional microbial exposure, diet and environment – strongly shape microbiome compositions [16].

Together, these cross-sectional studies established that the gut microbiome can influence ICI response, yet substantial variability across cohorts challenges the notion of universal microbial biomarkers across diverse environments and geographies.

To illustrate how strongly the environment-dependent microbiome can affect immunological readouts, it is worth recalling the example where immune phenotypes observed in laboratory mice could not be reproduced in wild mice. These discrepancies were traced back to differences in the murine skin microbiome [17].

Such geography- and environment-driven heterogeneities in cross-sectional studies have prompted a shift toward longitudinal designs with serial sampling before and during therapy. Shifting the focus from intercohort to intraindividual comparisons may allow the microbiome to be exploited for ICI response while circumventing geography-driven discrepancies.

Björk et al. [18] conducted the largest longitudinal study to date, including 175 patients with melanoma treated with anti-PD-1 or combination therapy. They also identified distinct microbial genome bins and pathways at baseline and during treatment that were linked to durable responses (PFS≥12 months) [18].

Macandog et al. [19] found that patients with durable response to anti-PD-1 therapy had stable microbiome functions. They further identified flagellin-related Lachnospiraceae peptides that mimic tumor antigens and may enhance anti-tumor immunity [19].

Microbial intervention

Early-phase clinical trials demonstrate the translational potential of microbiome modulation in advanced melanoma: Multiple fecal-microbiota-transplant-based studies – including trials in anti-PD-1-refractory [20, 21] and treatment-naïve patients [22] – have shown that transplantation of healthy-donor microbiota can safely induce favorable immune remodeling, enable donor-strain engraftment, and restore or augment responsiveness to PD-1 blockade. Across these trials, objective response rates of up to 65%, prolonged progression-free and overall survival, and durable complete responses underscore the promise of microbiome modulation as a therapeutic co-driver in melanoma [20–23]. Collectively, these data position microbiome-targeted interventions as an emerging strategy to overcome resistance and refine precision immuno-oncology.

Other microbiome sites

While most research in the context of ICI response and its association with the human microbiome has focused on the gut commensals, little is known about other microbial niches.

The skin microbiome may play a particularly important role in melanoma, although current evidence remains limited and complicated by strong variation across body sites. Early findings suggest that skin commensals such as

Staphylococcus epidermidis and *Cutibacterium acnes* may influence melanoma development [24].

Microbes can enter solid tumors via multiple routes [24]; and melanoma is known to harbour a distinct intratumoral microbiome compared to other malignancies [25]. It therefore seems plausible that the intratumoral microbiome in skin cancers could be shaped, at least in part, by the surrounding skin microbiome.

To develop reliable guidelines for integrating microbiome analysis into the daily clinical routine, future studies will need to adopt large-scale, longitudinal, and multi-specimen approaches [26]: Other microbiomes such as the intracellular intratumoral/intrametastatic commensals might show more promising associations with ICI response than the gut microbiome [25, 27], given their spatial proximity and potential for direct modulation of local anti-tumor immunity. Moreover, if it turns out that the microbial signatures in urine, blood [26] and saliva [10] could serve as robust biomarkers for ICI response, their use could greatly facilitate clinical implementation, as they are less complex to obtain and easier to process (Figure 1).

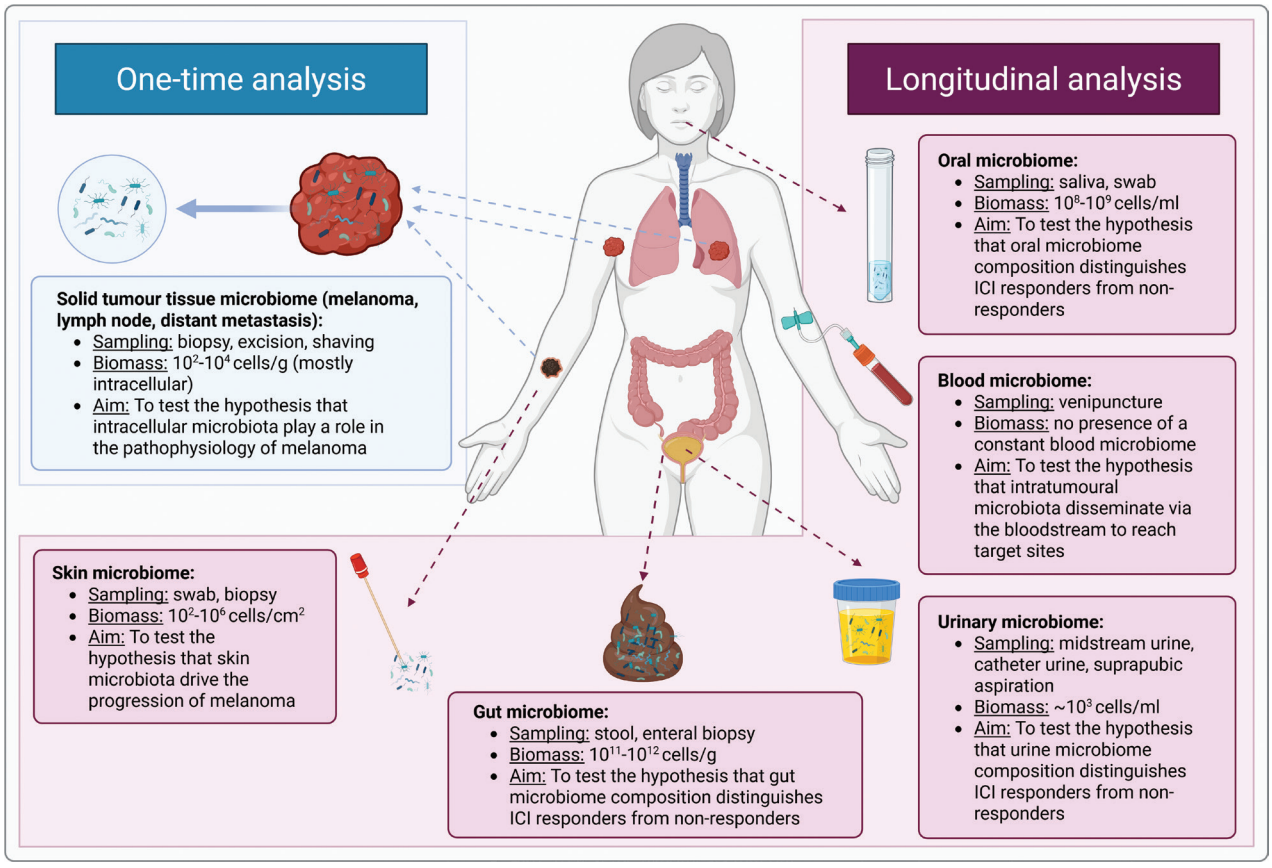

Figure 1. Microbiome on different body sites and their potential role in the pathophysiology of melanoma.

Potential mechanisms of microbiome-mediated immunemodulation

Innate immunity

By expressing multiple ligands for pattern recognition receptors (PRR), including toll-like receptors (TLR) and the stimulator of interferon genes (STING) pathway, commensals can modulate antigen-presenting cell (APC) activity and thereby significantly influence host immunity [26]. For instance, during

CTLA-4 inhibition *Bacteroides fragilis* activates TLR2-4 signaling, leading to IL-12 release and an enhanced anti-tumor response [8]. As another example of microbiome-driven modulation of innate immunity, c-di-AMP acts as a STING agonist, inducing type I interferon (IFN-I) release by intratumoral monocytes, which in turn promotes natural killer (NK) cell activation within the tumor microenvironment [28].

Adaptive immunity

There are more data on the link of microbiome composition and adaptive immunity. Distinct microbial genera and species of the gut microbiome may be associated with increased cytotoxic T-cell infiltration of tumors [10]. A more mechanistic perspective is provided by Kalaora et al. [27] who demonstrated that bacterial peptides derived from intracellular microbiota in metastatic melanoma cells can bind to MHC class I and II complexes, thereby enhancing tumor recognition and anti-tumor-immunity [27]. Other studies have shown that anti-tumor immunity can also be mediated via microbial metabolites: For example, inosine enhances IL-12 production by dendritic cells, thereby supporting T-cell activation as well as cytotoxic T-cell differentiation [29]. Another microbiome-dependent immunomodulatory variable, short-chain fatty acids (SCFAs), has been discussed controversially in recent years: On the one hand, it has been reported that butyrate can contribute to enhanced anti-tumor immunity via activation of cytotoxic memory T-cells [30]. On the other hand, elevated serum levels of butyrate and propionate have been linked to increased numbers of regulatory T-cells (Tregs) and, importantly, to resistance against CTLA-4 blockade [31]. Adaptive immunity may also be influenced by microbiome-dependent regulation of the intestinal immune checkpoint mucosal addressing cell adhesion molecule-1 (MAdCAM-1). Loss of MAdCAM-1, induced by antibiotic treatment or increased relative abundance of the genus *Enterocloster*, results in the release of Tregs from gut-associated lymphoid tissue (GALT) into tumor-draining lymph nodes and tumor beds, thereby impairing the response to PD-1 blockade [32].

Outlook & perspectives

Initial studies suggested that the gut microbiome might provide universal biomarkers for ICI response. However, larger and more powerful studies showed strong variability between cohorts, making such one-size-fits-all markers unlikely.

Other niches, such as the intratumoral microbiome, may be even more relevant for local immunity than the gut microbiome. At the same time, microbial markers of the skin, blood, saliva, or urine could simplify testing in clinical practice.

The next step should be the deep, systematic, longitudinal characterization of different microbiome sites across diverse melanoma patient populations.

Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

Not applicable.

Use of AI

During the preparation of this work the authors used ChatGPT in order to enhance readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Author contributions

Conceptualization: PW, JW. Investigation: JW, PW, CMR, HS. Supervision: PW, VS, RHW. Visualization: JW. Writing – original draft: JW. Writing – review and editing: VS, RHW, PW, HS, CMR.

Data availability

All of the data that support the findings of this study are available in the main text.

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